REMARKS

Claims 1-5, 9-18, and 22-28 are in this application. Claims 1, 4, 10, 11 and 17 have been amended. Claims 24, 25, 27 and 28 are withdrawn.

Claims 1 and 11 have been amended to include subject matter concerning some deleted limitations relating to the position of mismatches that was deleted in a previous amendment. .

In addition, claim 1 is amended to include:

> "wherein only one or more nucleotides at the 3'-end of the sense strand of the double-stranded part, and only one nucleotide located at position 11-13 from the 3'-end of the sense strand of the double-stranded part are not complementary to the antisense strand."

Claim 11 is amended to include:

> "wherein only one or more nucleotides at the 5' end and the 3' end of the sense strand of the double-stranded part, and only one nucleotide located at position 11-13 from the 3' end of the sense strand of the double-stranded part are not complementary to the antisense strand."

Support for these amendments is found, *inter alia,* throughout the specification. This was added to identify mismatches at the specified positions. Specifically, the dsRNA of claim 1 must have a mismatch(es) on the consecutive positions at 3'-end of the sense strand of the double-stranded part, and may optionally have one mismatch on the position located at position 11-13 from the 3'-end of the sense strand of the double-stranded part. The dsRNA of claim 11 must have a mismatch(es) on the consecutive positions at 5'-end of the sense strand of the double-stranded part, and may optionally have a mismatch(es) on the consecutive positions at 3'-end of the sense strand of the double-stranded part, and may optionally have one mismatch on the position located at position 11-13 from the 3'-end of the sense strand of the double-stranded part.

These amendments to claims 1 and 11 were added in order to exclude mismatches at any positions other than the specified positions.

The specification describes that the present invention relates to an siRNA so improved to control its effect on suppressing the gene expression (paragraphs [0008] and [0009]). A conventional siRNA, i.e. an siRNA before improvement, is described to have a sense and an antisense strands which are completely complementary to each other (paragraph [0019]). The siRNA of the present invention is described to be improved based on the conventional siRNA in that a mismatch(es) is introduced into one or more residues at the ends of the double-stranded part and/or only one residue at position 11-13 from the 3'-end of the sense strand of the double-stranded part (paragraphs [0008] and [0022] through [0030]). In particular, in paragraph [0008] it is stated that "The present inventor has found that in siRNA, the effect of siRNA on suppressing the gene expression is enhanced by introducing mismatches with (corresponding to) the antisense strand in several nucleotides at the 3'-end of the sense strand in the double-stranded part. Further, the present inventor has found that in siRNA, the effect of siRNA on suppressing the gene expression is reduced by introducing mismatches with (corresponding to) the antisense strand in several nucleotides at the 5'-end of the sense strand in the double-stranded part. The present invention is based on these findings" (emphasis added). Further, the specification provides no descriptions and no examples for a mismatch(es) present at other position(s). Therefore, the amendment is supported by the specification.

Claims 1 and 11 have been amended to replace the phrase "improved based on a conventional siRNA" with "improved as compared to a conventional siRNA" as suggested by the Examiner.

Claim 10 is amended to include the term "each strand" as found in claim 23.

According to the action, claims 1-5, 9-18, 22-23 and 26 are rejected under 35 USC 112, first paragraph. This is respectfully traversed.

It is applicants' position that this rejection is moot in view of the amended claims.

Therefore, it is respectfully requested that this rejection be withdrawn.

According to the action, claim 1 and all dependent claims 2-5, 9-18, 22-23 and 26 are rejected under 35 USC 112, second paragraph. This is respectfully traversed.

It is applicants' position that this rejection is moot in view of the amended claims.

Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 1 to 5, 9 to 18, 22, 23 and 26 as being anticipated by Zamore et al. (US 2005/0186586) as evidenced by Aravin and Elbashir. This is respectfully traversed.

The Examiner asserts that the claimed dsRNA is disclosed in Fig. 6A of Zamore et al..

In amended claim 1, the position(s) of a mismatch(es) is limited to one or more consecutive residues at the 3' end of the sense strand of the double-stranded part, and only one residue at position 11-13 from the 3'-end of the sense strand of the double-stranded part. In amended claim 11, the position(s) of a mismatch(es) is limited to one or more consecutive residues at the 5' end and the 3' end of the sense strand of the double-stranded part, and only one residue at position 11-13 from the 3'-end of the sense strand of the double-stranded part. In this regard, the phrase "one or more nucleotides in order from the 3'-end (or 5'-end) of the sense strand" means clearly that the one or more nucleotides are consecutive in view of the description of paragraphs [0008], [0022], [0024] and [0028] of the present specification. Specifically, paragraph [0008] describes "The present inventor has found that in siRNA, the effect of siRNA on suppressing the gene expression is enhanced by introducing mismatches with (corresponding to) the antisense strand in several nucleotides at the 3'-end of the sense strand in the double-stranded part." According to paragraph [0022] "The double-stranded RNA molecule according to a first aspect of the present invention is designed such that; in the abovementioned double-stranded RNA molecule, one or more nucleotides in order from the 3'-end of the sense strand of double-stranded part in said RNA molecule are not complementary to the antisense strand. Namely, the sense strand of the double-stranded RNA molecule according to the first aspect possesses one or more mismatches with the antisense

strand in order from the 3'-end of double-stranded part of the sense strand." (emphasis added). Claims 1 and 11 make it clear that the mismatches occur only at the specified positions.

Further, the present inventor has found that in siRNA, the effect of siRNA on suppressing the gene expression is reduced by introducing mismatches with (corresponding to) the antisense strand in several nucleotides at the 5'-end of the sense strand in the double-stranded part. The present invention is based on these findings. The Example section describes the examples of the claimed dsRNA (Tables 1 and 2). Accordingly, the amended claims should exclude any mismatches present at any positions other than one or more consecutive residues at the 3' end or 5'-end of the sense strand of the double-stranded part, and only one residue at position 11-13 from the 3'-end of the sense strand of the double-stranded part.

Fig. 6A of Zamore et al. does not disclose any dsRNA which meets the claimed limitations. In particular, the Examiner picked up three dsRNAs provided in Fig. 6A of Zamore et al.: miR-6-3, miR-13b-2, and miR-124a. MiR-6-3 and miR-124a have several mismatches which do not continue from any of the ends of the double-stranded part, and thus, do not fall within the scope of the claims. MiR-13b-2 has only one mismatch around the center of the double-stranded part, but the mismatch is not at position 11-13 from the 3'-end of the sense strand of the double-stranded part. Therefore, miR-13b-2 does not fall within the scope of the claims.

The claimed dsRNA is defined as being capable of suppressing the expression of a target gene in a cell by RNAi, which is generally called "siRNA," and is defined as being improved such that the dsRNA contains a mismatch(es) between sense and antisense strands thereof.

On the other hand, Fig. 6A of Zamore et al. discloses the dsRNAs consisting of miRNA and the opposite strand thereof, which are deduced to be generated by Dicer cleavage of naturally-occurring miRNA precursors (paragraphs 0019 and 0287 of Zamore et al.). Please note that the term "siRNA" found in paragraph 0019 means an siRNA-like duplex which may be formed if the miRNA precursor is cleaved by Dicer into an siRNA duplex-like structure, in view of paragraph 0287. Therefore, Fig. 6A of Zamore et al. discloses miRNAs, not siRNAs.

As shown in paragraph 0003 of Zamore et al., siRNA and miRNA commonly trigger post-transcriptional gene silencing, but belong to different types of RNA generated by different

processes. Further, the miRNA has been known to control the translation of a target gene, and to be different from the siRNA in that it causes gene silencing with no degradation of the target mRNA (see, for example, page 6877, the right column, the 3rd paragraph of Elbashir et al., EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001, which is cited by the Examiner in the outstanding Action). Please note that the term "stRNA" (small temporal RNA) found in Elbashir et al. means miRNA (see, for example, paragraph 0080 of Zamore et al.). Therefore, miRNAs are clearly distinguished from siRNAs in the developments and functions thereof.

Accordingly, Fig. 6A of Zamore et al. does not disclose siRNA, i.e., dsRNA which is capable of suppressing the expression of a target gene in a cell by RNAi.

In addition, the dsRNAs disclosed in Fig. 6A of Zamore et al. are deduced to be generated by Dicer cleavage of naturally-occurring miRNA precursors (paragraphs 0019 and 0287 of Zamore et al.). Therefore, the mismatches found between sense and antisense strands of the dsRNAs are to be generated naturally, but not artificially introduced (improved).

Accordingly, Fig. 6A of Zamore et al. does not disclose dsRNA which is improved such that the dsRNA contains a mismatch(es) between sense and antisense strands thereof.

Consequently, the claimed dsRNA is not disclosed in Fig. 6A of Zamore et al..

Therefore, it is respectfully requested that the rejection be withdrawn.

The Examiner has rejected claims 1 to 5, 9 to 18, 22, 23 and 26 as being obvious over Jayasena et al. (US 2004/0248299), Khvorova et al. (US 2007/0031844), Elbashir et al. (EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), and Holen et al. (Nucleic Acids Research, 2002, Vol. 30, No. 8, pp. 1757-1766). This is respectfully traversed.

An important technical feature of the present invention is introduction of a mismatch(es) into a sense strand of siRNA. An antisense strand of the claimed siRNA should be designed in a conventional manner, and thus, should be completely complementary to a sense strand of the target mRNA. This technical feature is neither described nor suggested in any of the citations.

The Examiner asserts that those skilled in the art would have conceived to incorporate mismatches at the ends of the siRNA in view of Jayasena et al. and Khvorova et al.. Regarding possibility of degradation of siRNA at the single-stranded part, the Examiner comments that the mismatches at the ends of the dsRNA are designed such that the duplex region is associated but that the association between the mismatched bases is weaker to allow for unwinding and preferential loading of the proper guide strand into RISC therefore the ends are not single stranded.

It is applicants' position that this statement by the Examiner is based on hindsight. Those skilled in the art would have expected that mismatches at the ends of siRNA would cause a single-stranded part which may be degraded by RNase in a cell, resulting in very low efficiency of RNAi. In fact, Jayasena et al. and Khvorova et al. did not try to do so although the procedure therefor was not so complicated.

In addition, the Examiner points out that it was well known in the art that incorporation of chemical modifications of dsRNA molecules protected the molecule against degradation by nucleases. However, this knowledge could never provide those skilled in the art with any motivation for introduction of mismatches into a siRNA molecule.

Further, the Examiner believes that Elbashir et al. and Holen et al. disclose effect of mismatches introduced into siRNAs on RNAi.

However, the mismatches disclosed in Elbashir et al. and Holen et al. are between the antisense strand of siRNA and the target mRNA.

Specifically, in the siRNA molecules disclosed in Elbashir et al. and Holen et al., a sense strand does not contain any mismatches to the target mRNA, and an antisense strand contains a mismatch to the target mRNA. On the other hand, in the siRNA molecule according to the present invention, an antisense strand does not contain any mismatches to the target mRNA, and a sense strand contains a mismatch to the target mRNA.

In addition, Elbashir et al. and Holen et al. introduced a mismatch into an antisense strand of an siRNA molecule in order to investigate the sequence specificity of RNAi and the tolerance of RNAi system for mismatches. On the other hand, in the present invention, a mismatch is

introduced into a sense strand of an siRNA molecule in order to modulate the efficiency of RNAi.

Therefore, Elbashir et al. and Holen et al. could never provide any suggestions for the technical feature of the present invention.

There is no combination of the cited references that teaches, suggests or provides one of skill in the art with the suggestion of the claimed invention. Therefore, it is respectfully requested that this rejection be withdrawn.

If any additional fees are due, please charge deposit account 12-0425.

It is submitted that the application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

JANET I. CORD
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.33778 (212)708-1935

JIC/cgt